REMARKS

Reconsideration of this application is requested.

At the outset, the undersigned wishes to thank the Examiner (Mr. Rizzo) for kindly agreeing to conducting a further personal interview on this application. The interview was held on February 7, 1996, and the courtesies extended by the Examiner were most appreciated.

I. THE FORMAL REJECTION

Claims 1-25 have been rejected under 35 USC 112, first and second paragraphs, on the ground that the definition of "X" is not sufficiently definite. This rejection was discussed in some detail during the interview. As a result of that discussion, and in response to the rejection, claim 1 has been cancelled and replaced by new claim 35 which has been arrived at by combining claims 1 and 2. For consistency, method claim 17, the other independent claim in the case, has also been cancelled and replaced by new method claim 36 which has been arrived at by combining previous claims 17 and 20. Claim 20 has consequently been cancelled, as has claim 10 which was dependent on previous claim 2. The subject matter of cancelled claim 10 is encompassed by claim 9 which is dependent on new claim 35.

In new claim 35, the structural residue androsta-3,5-dien-3-ol which was not listed in claim 2 has been added to the list. Basis for this addition appears in Example 11.

New claims 35 and 36 are now believed to be in full compliance with 35 USC 112, first and second paragraphs. The compounds are completely defined both from

the standpoint of "X" (derived from claims 2/20) and the remainder of the substituents R and R^{14} through R^{16} (defined as in original claim 1). The dependent claims have been amended to reflect the addition of new claims 35 and 36.

Attention was also directed during the interview to the working examples contained in the application, and Table 2 (pages 37-38), which show the enzyme inhibitory effects of the compounds of the invention with respect to numerous different steroid structures, including 7 different A-rings (Examples 1, 2, 3, 4, 6, 8 and 9), four different B-rings (Examples 1, 4, 12 and 13) and a different C-ring (Example 10). More than adequate exemplification is therefore provided in the present specification for the invention as claimed in its current scope.

The requested claim revisions are clearly supported by the originally-filed application and do not constitute the introduction of new matter. Entry of the new and amended claims is therefore in order and is requested.

The Examiner indicated informally during the interview that amendment of the claims in this way would obviate the outstanding formal rejection. Reconsideration and withdrawal of the 35 USC 112 rejection is now respectfully requested.

II. THE OBVIOUSNESS REJECTION

The claims have again been rejected under 35 USC 103 as unpatentable over Wicha et al for the reasons set forth in the previous official action. That rejection is traversed for the following reasons.

(a) **The Invention**

The present invention is directed to a class of 17-pyridyl steroids which act as hydroxylase-lyase inhibitors. The present inventors have discovered in particular that hydroxylase-lyase inhibitory activity is possessed only when the nitrogen atom of the pyridyl ring is in the 3-(or meta) position relative to the point of attachment of the pyridyl ring to the steroid residue, and when the steroid molecule possesses 16,17-unsaturation. The claims in the case are directed to steroids *per se* possessing these structural features and to the method of using the compounds to treat androgen-dependent and estrogen-dependent disorders, especially prostatic cancer and breast cancer.

The compounds as claimed in claim 35 are novel. As noted in the specification at page 2 beginning at line 17, and explained during the interview, certain of the compounds have been disclosed as **intermediates** in the synthesis of certain steroids having a 3-pyridyl or a 3-pyridonyl group in the 17β-position. Those compounds are **excluded** from the claims directed to the compounds *per se*. There is no suggestion in the art that such excluded compounds are useful for treating androgen-dependent or estrogen-dependent disorders, and so the compounds disclosed as intermediates in the prior have not been excluded from the method of treatment claims 36 and 18-24 or from claim 35 directed to an orally ingestible solid composition comprising a compound of the invention in association with a pharmaceutically acceptable carrier or diluent. The intermediates are listed on page 2 line 17 through page 2 line 14 of the specification, and appear in the four Wicha papers AR. AS, AT and AU cited by the applicants. The Wicha paper AR is that relied on by the Examiner in the outstanding obviousness rejection.

The claimed compounds (excluding the Wicha synthesis intermediates) are non-obvious because the cited art fails to suggest that the compounds as claimed, having a 17-(3-) pyridyl group (i.e. one which has the pyridyl nitrogen atom in the 3-position relative to the point of attachment of the pyridyl ring to the steroid residue), together with 16,17-unsaturation. would be useful for the purpose described in the present application. Thus, the art relied upon fails to give rise to a *prima facie* case of obviousness of the claimed invention. Given that there is no *prima facie* case of obviousness, there is no need, for purposes of establishing patentability, to rely on secondary considerations, such as comparative evidence. The applicants have in fact provided evidence of unexpected results both in the originally filed specification and in the form a Rule 132 declaration (the Barrie Declaration). However, while such evidence is convincing, it is not necessary for purposes of establishing patentability. Patentability subsists in the compounds as claimed and used by virtue of their specific structural features and the unexpected pharmaceutical properties tied to those structural features.

(b) **The Cited Art**

Wicha fails to give rise to a *prima facie* case of obviousness against the presently claimed compounds and method. As noted earlier, the synthesis intermediates disclosed by Wicha are excluded from the scope of the compounds as claimed. Wicha is concerned with the synthesis of compounds (of formula (3)) alleged to have "cardiotonic" (i.e. able to stimulate the heart by increasing the force of myocardial contraction). The scheme shown on page 21 of AR describes the numerous intermediates involved in the synthesis of compounds of the formula (3) as shown on page 20 of Wicha. It will be seen that the structure of the final compound of formula (3), which allegedly possesses cardiotonic activity, bears **no** resemblance whatsoever to the compounds as claimed in the present application.

Thus, the compound of formula (3) on page 20 of Wicha possesses a **14β-hydroxy** substituent, and there is **NO unsaturation at the 16, 17-position of the D ring**. The presently claimed compounds do **NOT** possess a hydroxyl substituent at the 14-position and **DO** possess 16, 17-unsaturation, unlike the Wicha compounds of formula (3).

In light of the above, it is believed that claim 35 directed to the compounds *per se* and the compositions are clearly patentably distinguished over the cited Wicha teachings. No *prima facie* case of obviousness is generated by that reference.

Similar arguments apply with respect to the method of treatment claims. The art is completely silent with respect to the use of the compounds as now defined for treating androgen-dependent or estrogen-dependent disorders. Clearly, therefore, no *prima facie* case of obviousness arises with respect to the method of treatment claim 36 and claims dependent thereon. A person of ordinary skill would not have been motivated to rely on the Wicha teachings when seeking to solve the problem of developing compounds active as hydroxylase-lyase inhibitors and suitable for use in the treatment of androgen-dependent estrogen-dependent disorders because Wicha focuses on compounds allegedly having cardiotonic properties. Absent any such motivation, a *prima facie* case of obviousness has clearly not been made out. Reconsideration and withdrawal of the obviousness rejection on this ground alone is accordingly respectfully requested.

As noted earlier, patentability of the claimed invention is further established by evidence present in the originally filed application and that contained in the Barrie declaration submitted with the response of September 11, 1995. Since there is no *prima facie* case of obviousness in this case, the applicants do not need to rely on the evidence of record to further substantiate patentability. For completeness,

however, the evidentiary showing contained in the application and the Barrie declaration is summarized below.

Table 1 on page 5 of the specification demonstrates the enzyme inhibitory effect possessed by the presently claimed compounds. In that Table, enzyme activities are measured by IC_{50} figures, IC_{50} being the concentration of test compound required to achieve 50% enzyme inhibition. Thus, the lower the number in the column, the more effective is the test compound. It will be seen that the 3-pyridyl compound is roughly from 40 to 80 more effective than the 2-pyridyl counterpart and 700-1200 times more effective than the 4-pyridyl counterpart.

Table 2 on pages 37-38 of the specification shows that variations in the A, B and C rings of the steroid molecule have little effect on inhibition of hydroxylase and lyase. This evidence further establishes the importance of the structure of the D ring of the steroid molecule to achieving the desired properties, independent of the nature of the A, B and C rings.

The Barrie declaration focuses on the importance of 16,17-unsaturation in the compounds of the invention. The declaration describes tests conducted on a compound within the scope of claim 35 and its B-ring saturated analogue relating to inhibition of the 17α-hydroxylase-lyase enzyme. Compound (1) in the Table in paragraph 7 of the Barrie declaration is a compound of the invention; compound (2) is its D-ring saturated analogue. As will be seen from the results, the fall-off in inhibitory activity with D-ring saturation is in the region of 10-fold. A comparison is also shown for the corresponding 17-4-(pyridyl) compounds (3) and (4) where the reverse trend is seen, but the 4-pyridyl compound are relatively inactive.

The Examiner has raised a number of specific points in the action relating to the Barrie declaration. The following comments are offered on the Examiner's points but, as noted during the interview, and as stressed in the present response, patentability of the presently claimed compounds and method is not dependent on the evidence of record in this case. The cited art fails to give rise to a *prima facie* case of structural obviousness, and so the secondary evidence of record, while convincing and commensurate, is not essential to a holding of patentability in this case. The closest prior art compounds are excluded from the claimed invention. Moreover, those closest prior art compounds are disclosed in the prior art as **synthesis intermediates**, with no teaching or suggestion in the art that they possess any pharmaceutical utility. The **ultimate** compounds which are produced by the prior art using the **synthesis intermediates** are structurally remote from the presently claimed compounds and are described as having a utility (cardiotonic properties) which is also remote from the utility described and claimed in the present application. In this regard, the Examiner's attention is directed to the response previously filed in this case on September 11, 1995 and, in particular, the discussion appearing at page 3 last line through to page 11 (herein incorporated by reference). The evidence presented in the form of published literature references with that response clearly establishes that **BOTH** a 14β-hydroxy group **AND** 16,17 saturation are essential to achieving cardiotonic properties. The presently claimed compounds contain **NEITHER** of these structural features.

For all of the above reasons, the outstanding obviousness rejection should now be withdrawn. Such action is respectfully requested.

III. ADMINISTRATIVE MATTERS

During the interview, the Examiner was requested to initial the PTO 1449 which accompanied the response of September 11, 1995 and to return a copy of the initialed document to the undersigned. The Examiner indicated that the PTO 1449 is in the file. It is requested that a copy of the initialed document be returned to the undersigned with the next paper to issue in this case.

The Examiner has not acknowledged receipt of the certified priority documents for this application. Acknowledgment is requested in the next paper to issue in the case.

Allowance of the application is awaited.

Respectfully submitted,

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